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A monoclonal antibody-beta-glucuronidase conjugate as activator of the prodrug epirubicin-glucuronide for specific treatment of cancer.

Haisma HJ, Boven E, van Muijen M, de Jong J, van der Vijgh WJ, Pinedo HM.

Department of Medical Oncology, Free University Hospital, Amsterdam, The Netherlands.

The anti-pan carcinoma monoclonal antibody (MAb) 323/A3, linked to E. coli-derived beta-glucuronidase (GUS) was used to study the tumour-site-selective activation of the prodrug Epirubicin-glucuronide (Epi-glu). Epi-glu was isolated from the urine of patients treated with Epirubicin (Epi) by reversed phase chromatography on a silica-C18 column. Epi-glu was stable in human blood and was not converted into Epi by A2780, MCF-7, or OVCAR-3 cancer cells, despite the presence of intracellular GUS. The stability of the prodrug was confirmed in BALB/c mice. MAb 323/A3 and GUS were linked through a stable thioether bond. The conjugate (1:1) was purified by ion exchange and gel filtration chromatography. Binding to target cells revealed an immunoreactivity of at least 60% and good retention of enzyme activity. A protein dye (sulforhodamine B) assay was used to analyse cytotoxicity. Epi (IC50 of 0.003-0.2 microM) was 100-1,000 times more toxic than Epi-glu (IC50 of greater than 20 microM), when cancer cells were exposed for 4 or 24 h to the drugs. The low cytotoxicity of Epi-glu was most likely due to the reduced cellular uptake rate of the prodrug (2.7 pmol 10(-6) cells min-1) as compared to that of the parent compound (25 pmol 10(-6) cells min-1). Pretreatment of antigen-positive cells with the 323/A3-GUS conjugate prior to prodrug exposure completely restored cytotoxicity as a result from hydrolysis of Epi-glu into Epi. Our results demonstrate that the 323/A3-GUS conjugate can specifically activate the stable non-toxic prodrug Epi-glu at the tumour cell level.

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